COMMENTS AND RESPONSES

Insulin Resistance and Progression to Type 1 Diabetes in the European Nicotinamide Diabetes Intervention Trial (ENDIT)

Response to Bingley et al.

The accelerator hypothesis proposes that type 1 and type 2 diabetes are both driven by insulin resistance (1), and its principle prediction is an inverse correlation between BMI and age at onset in children with type 1 diabetes. Bingley et al. (2) examined ENDIT data and found evidence for an inverse correlation only among those with advanced β-cell loss (low first-phase insulin response) (FPIR). They conclude that insulin resistance has only a limited role to play in the later stages of β-cell destruction and that interventions designed to increase insulin sensitivity are unlikely to impact progression to diabetes in the longer term.

The conclusions are worthy of note given their provenance, but the argument may be flawed because the period of observation was too short. Age at presentation depends on tempo of progression, and it is likely that those of highest FPIR are those who progress most slowly. While the accelerator hypothesis is based on the long-term observation of whole populations with type 1 diabetes—those who progress slowly as well as those who progress quickly—the much briefer ENDIT study may have prejudiced its own findings by favoring those who progress quickly to the exclusion of those who progress slowly.

The authors recognize the shortcoming and concede that, given the follow-up of 5 years, "participants with higher FPIR may develop diabetes at a later date." Later diabetes in some is arguably predictable, since all were at high risk, and it is difficult to know what interpretation to place on this report.

There are now four independent studies, all based on whole populations observed over 20 years or more, that unequivocally demonstrate an inverse relationship between BMI and age at onset of type 1 diabetes. Until tested definitively, the accelerator hypothesis will stand or fall by the close scrutiny it has received here and elsewhere (3–5), but it is important that experimental conditions be appropriate. The ultimate test will be a randomized trial in which insulin sensitization is the intervention and conversion from risk to disease the outcome measure.

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References

1. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
2. Bingley PJ, Mahon JL, Gale EA, the European Nicotinamide Diabetes Intervention Trial (ENDIT) Group: Insulin resistance and progression to type 1 diabetes in the European Nicotinamide Diabetes Intervention Trial (ENDIT). *Diabetes Care* 31: 146–150, 2007
3. Wilkin TJ: The accelerator hypothesis cannot be tested using the type 2 diabetes gene, TCF7L2. *Diabetologia* 50:1780, 2007
4. Wilkin TJ: Testing the accelerator hypothesis: body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes-(Letter). *Diabetes Care* 29:1462–1464, 2006
5. Wilkin TJ: To boldly go—or to go too boldly? The accelerator hypothesis revisited. *Diabetologia* 50:1571–1575, 2007